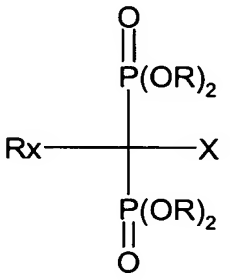
Amendments to the Claims:

Listing of the Claims:

Claim 1 (currently amended): A pharmaceutical preparation which comprises ~~in combination~~ a bisphosphonate of formula I, or a physiologically acceptable and –cleavable ester or a salt thereof



I

wherein

X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C_1-C_4 alkyl, or alkanoyl;

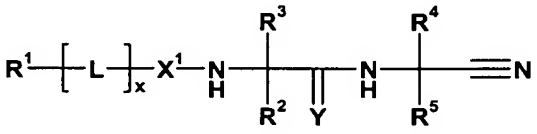
R is hydrogen or C_1-C_4 alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

or a pharmaceutically acceptable salt thereof or any hydrate thereof; ~~and~~

in combination with one of the following:

a) a cat K inhibitor of formula V, or a physiologically acceptable and –cleavable ester or a salt thereof



(V)

wherein R^1 is optionally substituted (aryl, aryl-lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl or heterocyclyl-lower alkyl);

R^2 and R^3 together represent lower alkylene, optionally interrupted by O, S or NR^6, so as to form a ring with the carbon atom to which they are attached, and R^6 is hydrogen, lower alkyl or aryl-lower alkyl;

R^4 and R^5 are independently H, or optionally substituted (lower alkyl or aryl-lower alkyl), -C(O)OR^7, or –C(O)NR^7R^8, wherein R^7 is optionally substituted (lower alkyl, aryl,

aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl), and R^8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl); or

R^4 and R^5 together represent lower alkylene, optionally interrupted by O, S or NR^6, so as to form a ring with the carbon atom to which they are attached, and R^6 is hydrogen, lower alkyl or aryl-lower alkyl; or

R^4 is H or optionally substituted lower alkyl and R^5 is a substituent of formula $-X^2-(Y^1)_n-(Ar)_p-Q-Z$ wherein

Y^1 is O, S, SO, SO_2, $N(R^6)SO_2$, N-R^6, SO_2NR^6, $CONR^6$ or NR^6CO;

N is zero or one;

P is zero or one;

X^2 is lower alkylene: or when n is zero, X^2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2, NR^6, SO_2NR^6, $CONR^6$ or NR^6CO, and R^6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

Z is hydroxyl, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sufonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y^1-lower alkylene or C_2-C_7-alkylene interrupted by Y^1;

X^1 is $-C(O)-$, -C(S)-, -S(O)-, $-S(O)_2-$, or $-P(O)(OR^6)-$, and R^6 is as defined above;

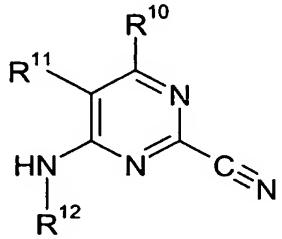
Y is oxygen or sulphur;

L is optionally substituted –Het-, -Het-CH_2- or $-CH_2$-Het-, and Het is a hetero atom selected from O, N or S; and

X is zero or one; and

aryl in the above definitions represents carbocyclic or heterocyclic aryl; or ~~alternatively~~

b) ~~another class of~~a cat K inhibitor~~s~~ of formula VII, or a physiologically acceptable and –cleavable ester or a salt thereof



VII

wherein

R^{10} is H, -R^{14}, -OR^{14} or $NR^{13}R^{14}$,
wherein R^{13} is H, lower alkyl or C_3 to C_{10} cycloalkyl, and
R^{14} is lower alkyl or C_3 to C_{10} cycloalkyl, and
wherein R^{13} and R^{14} are independently, optionally substituted by halo, hydroxy, lower alkoxy, CN, NO_2, or optionally mono- or di-lower alkyl substituted amino;
R^{11} is –CO-N R^{15} R^{16}, -NH-CO- R^{15}, -CH_2-NH-C(O)-R^{15}, -CO- R^{15}, -S(O)- R^{15}, -$S(O)_2$-R^{15},-CH_2-CO- R^{15} or -CH_2-N R^{15} R^{16},
wherein
R^{15} is aryl, aryl–lower alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl,
R^{16} is H, aryl, aryl–lower alkyl, aryl-lower-alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl, or
wherein R^{15} and R^{16} together with the nitrogen atom to which they attached are joined to form an N-heterocyclyl group,
wherein N-heterocyclyl denotes a saturated, partially unsaturated or aromatic nitrogen containing heterocyclic moiety attached via a nitrogen atom thereof having from 3 to 8 ring atoms optionally containing a further 1, 2 or 3 heteroatoms selected from N, NR^{17}, O, S, S(O) or $S(O)_2$ wherein R^{17} is H or optionally substituted (lower alkyl, carboxy, acyl (including both lower alkyl acyl, e.g. formyl, acetyl or propionyl, or aryl acyl, e.g. benzoyl), amido, aryl, S(O) or $S(O)_2$), and wherein the N-heterocyclyl is optionally fused in a bicyclic structure, e.g. with a benzene or pyridine ring, and wherein the N-heterocyclyl is optionally linked in a spiro structure with a 3 to 8 membered cycloalkyl or heterocyclic ring wherein the heterocyclic ring has from 3 to 10 ring members and contains from 1 to 3 heteroatoms selected from N, NR^{16}, O, S, S(O) or $S(O)_2$ wherein R^{16} is as defined above), and
wherein heterocyclyl denotes a ring having from 3 to 10 ring members and containing from 1 to 3 heteroatoms selected from N, NR^{17}, O, S, S(O) or $S(O)_2$ wherein R^{17} is as defined above), and
wherein R^{15} and R^{16} are independently, optionally substituted by one or more groups, e.g. 1-3 groups, selected from halo, hydroxy, oxo, lower alkoxy, CN or NO_2, or optionally substituted (optionally mono- or di-lower alkyl substituted amino, lower-alkoxy, aryl, aryl-lower alkyl, N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein the optional substitution comprises from 1 to 3 substituents selected from halo, hydroxy, lower alkoxy, lower alkoxy-lower alkyl, lower alkoxy-carbonyl, CN, NO_2, N-heterocyclyl or N-heterocyclyl-lower alkyl, or optionally mono- or di-lower alkyl substituted amino;

R^{12} is is independently H, or optionally substituted (lower alkyl, aryl, aryl–lower alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl), and

wherein R2 is optionally substituted by halo, hydroxy, oxo, lower alkoxy, CN, NO_2, or optionally mono- or di-lower alkyl substituted amino.

for simultaneous, sequential or separate use.

Claim 2 (currently amended): The pharmaceutical preparation according to claim 1[[;]] ~~whereas~~ wherein its use is for the treatment of malignant diseases, bone metastasis, cancer cell growth, or/and cancer therapy-induced bone loss.

Claim 3 (currently amended): ~~The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a malignant disease, bone metastasis, cancer cell growth or/and cancer therapy-induced bone loss; or~~

~~a~~ A method of treating a patient suffering from a malignant disease, bone metastasis, cancer cell growth, or/and cancer-therapy-induced bone loss comprising administering to the patient an effective amount of ~~a bisphosphonate~~the pharmaceutical preparation according to claim 1 ~~and an effective amount of a cathepsin K inhibitor according to claim 1~~.

Claim 4 (currently amended): ~~The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a benign disease, bone loss disease, osteoporosis, osteoarthritis; or~~

~~a~~ A method of treating a patient suffering from a benign disease, bone loss disease, osteoporosis, osteoarthritis comprising administering to the patient an effective amount of ~~a bisphosphonate~~the pharmaceutical preparation according to claim 1 ~~and an effective amount of a cathepsin K inhibitor according to claim 1~~.

Claim 5 (currently amended): A pharmaceutical composition comprising ~~Zoledronic~~ zoledronic ~~Acid~~ acid and a cathepsin K inhibitor for the inhibition of bone metastasis, cancer cell growth or/and inhibition of cancer-therapy-induced bone loss.

Claim 6 (currently amended): A pharmaceutical preparation according to claim 1 ~~or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition of claim 5~~, in which the cathepsin K inhibitor is selected from the group of N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-ethyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-isopropyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-benzyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-propyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]- 4-[1-(2-methoxy-ethyl)-piperidin-4-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-isopropyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-cyclopentyl -piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-methyl-piperidin-4-yl)-benzamide, and N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(1-propyl-piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-propyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-2,2-dimethyl-3-[4-(4-methyl-piperazin-1-yl)-phenyl]-propionamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-2,2-dimethyl-3-[3-(4-methyl-piperazin-1-yl)-phenyl]-propionamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-ethyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-isopropyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-piperazin-1-yl-benzamide, 4-(4-{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-carbamoyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester, 4-(3-{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-carbamoyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-ethyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-

ylmethyl]-3-(4-isopropyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(2-dimethylamino-ethoxy)-4-methoxy-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-dimethylaminomethyl-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-ylmethyl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-piperidin-1-yl-ethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(4-ethyl-piperazin-1-yl)-phenyl]-2,2-dimethyl-propionamide or pharmaceutically acceptable salt thereof.

Claim 7 (currently amended): A pharmaceutical preparation according to claim 1 ~~or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition according to claim 5~~, in which the cat K inhibitor is N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-(1-propyl)-piperazin-1-yl)-benzamide or a pharmaceutically acceptable salt thereof and the bisphosphonate is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or pharmacologically acceptable salts thereof.